A Current Update on the Use of Alpha Lipoic Acid in the Management of Type 2 Diabetes Mellitus

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Abstract: Type 2 Diabetes Mellitus (T2DM) which is characterised by insulin resistance, is closely linked to the triad of glucolipotoxicity, inflammation and oxidative stress. Increased adiposity, leading to increased free fatty acids (FFAs), contributes to insulin resistance by disrupting the signal transduction pathway of insulin mediated glucose disposal, and causes impaired insulin secretion. Hyperglycaemia and dyslipidaemia driven oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defence is implicated in the pathogenesis of diabetic neuropathy (DN). This and other inflammatory pathways account for a complex network of interacting metabolic factors responsible for causing diabetes and her complications. There is growing evidence that Alpha Lipoic Acid (ALA) has beneficial effects on the treatment of T2DM and some of its complications. It represents an attractive pharmacological target in the treatment of T2DM by modulating the signal transduction pathways in insulin resistance and antagonizing the oxidative and inflammatory stresses, which are major players in the pathogenesis of this disorder. A potent anti-oxidant and free radical scavenger, ALA also targets cellular signal transduction pathways which increases glucose uptake and utilization, thus providing specific targeted therapy in the treatment of insulin resistance and diabetic neuropathy. Apart from the rare risk of Insulin Autoimmune Syndrome (IAS), ALA has shown to be relatively safe, even in patients with renal and liver failure. This review focuses and summarises the molecular mechanisms of T2DM, and underlines the therapeutic value of ALA in this globally significant disease.

Key Words: ALA, anti-oxidant, diabetes, neuropathy, radical, insulin resistance.

INTRODUCTION

Alpha Lipoic Acid (ALA), also known as thiotic acid in Europe, is an 8-carbon, cyclic disulfide thio-octanoic acid that was first described by Lester in 1951 [1].

Having an asymmetric carbon atom, ALA has two isomers, R-enantiomer (R-LA) and S-enantiomer (S-LA). Only the R-isomer is endogenously synthesized and bound to protein. R-LA, being an essential cofactor for the biogenesis of mitochondrial enzymes, is found as a naturally occurring prosthetic group in the alpha-keto acid and pyruvate dehydrogenase complexes and is both easily taken up into cells, as well as being a fundamental player in metabolism [2-4].

ROLE IN OXIDATIVE STRESS

Oxidative stress, characterized by a persistent imbalance between the production of highly reactive- reactive oxygen species (ROS) and reactive nitrogen species (RNS) and anti-oxidant defences, leads to an altered cellular redox status and subsequent tissue damage [5, 6]. It was defined by Seis as a change in the pro-oxidant/anti-oxidant balance, in favour of the former, potentially leading to biological damage [7]. This biological damage, which includes DNA mutations and modifications to proteins and lipids, has been shown to be responsible for many modern diseases like cancer, cardiovascular disease, diabetes mellitus and even ageing.

The free radical theory of ageing by Harman introduced the idea that endogenous free radicals produced by cells results in the accumulation of cellular damage [8, 9]. However, it was Ozawa's theory of redox mechanism of mitochondrial ageing which highlighted the importance of the mitochondria as an important source of ROS which usually occurs as a result of electron leakage in complexes I and III of the electron transport chain [10]. Mitochondria DNA has no histone protection or efficient repair system and is prone to the accumulation of DNA damage, which further lowers the bioenergetic capacity of mitochondria, resulting in a vicious cycle of increasing ROS production [11, 12].

While anti-oxidants serve to limit this damage, ALA contributes to the defence against oxidative stress by increasing the synthesis of anti-oxidants like glutathione, one of the most abundant intra-cellular anti-oxidants in the body [13, 14]. There is also evidence that ALA has the ability to directly scavenge ROS and RNS. Furthermore, the reduced form of ALA, dihydrolipoic acid (DHLA), *via* its reducing property, has the ability to reduce the oxidized form of other anti-oxidants such as ascorbic acid, alpha-tocopherol and coenzyme Q10 [15-17]. Hence, ALA has the theoretical potential to 'perpetuate' its antioxidant effect even after it is cleared systemically from the plasma, and thus plays a vital role in the regulation of other antioxidants and the synergism of antioxidants as a whole, described by Packer *et al.* [15] as the body's "antioxidant network". In addition, other yet unknown downstream actions of ALA with effects on this network may persist long after ALA has been cleared from the system.

Finally, ALA possesses metal chelating capacities which has been shown to reduce iron and copper mediated oxidative damage *in vitro* [18, 19], and reverse age-related iron

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accumulation and anti-oxidant depletion in the rat cerebral cortex [20]. Hence, the ability of ALA to alter the redox status of cells and interact with other antioxidants provides an attractive therapeutic potential in conditions where oxidative stress is involved [21].

ROLE IN SIGNAL TRANSDUCTION

Another important role of ALA is in the area of signal transduction. ALA acutely activates insulin receptors (IR) in its reduced state, which leads to a cascade of substrate phosphorylation that causes the translocation of glucose transporters (GLUT) from the cytoplasm to the cell surface. This results in peripheral glucose disposal, and a defect at any point in this pathway can lead to insulin resistance [22, 23].

ALA is also involved in the regulation of the nuclear factor-kappa B (NF-kB) and Akt signaling pathways [24]. NF-kB has been shown to regulate genes related to inflammation and cell cycle control, which have been implicated in the development of atherosclerosis, insulin resistance, pancreatic β cell cycle and even increasing chemosensitivity of mitotic lesions [25]. Results of cell line studies have shown that physiologic amounts of ALA inhibit NF-kB nuclear translocation, thus preventing its downstream effects on target gene expression [26]. ALA offers the potential for improved molecular therapeutic strategies.

PHARMACOKINETICS

ALA is soluble in both water and organic solvents [15]. A few studies demonstrated that up to 30-40% of orally ingested racaemic ALA is absorbed with peak plasma concentrations higher in the R-isomer compared to the S-isomer, suggesting better absorption in the former as well as in a fasted state [27, 28].

That ALA is both soluble in water and organic solvents is significant, because although studies have shown no significant tissue accumulation and free plasma ALA levels after an oral ingestion is almost negligible due to rapid clearance rate, ALA is able to exert its powerful antioxidant effects because of this unique amphiphilic property. Because it is both hydrophobic and hydrophilic, it is able to elicit antioxidant effects by scavenging ROS and RNS in both media of cells and blood i.e. hydrophilic (cytoplasm and serum) and hydrophobic (plasma membrane and lipoprotein) [29]. Boreca *et al.* demonstrated a decrease in oxidative stress in diabetic patients on ALA treatment compared to those that were not, by measuring the plasma lipid hyperoxide: (alpha tocopherol/cholesterol) ratio. This was found to be independent of poor glycaemic control and albuminuria [30].

Relatively little is known regarding the excretion of ALA, except that renal excretion does not appear to play a significant role, and it has been shown to be safe in patients with End-Stage Renal Failure (ESRF) as well as in liver disease [31-33]. In fact, it has been used in the treatment of chronic hepatitis C, metal intoxication and liver damage secondary to alcohol, Amanita mushrooms [34], and carbon tetrachloride (CCl4) with encouraging results [35].

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 Diabetes Mellitus (T2DM) especially in the early stages, is characterized by insulin resistance secondary to the triad of glucolipotoxicity, inflammation and oxidative stress. Increased adiposity, thought to be one of the initiating events, results in increased free fatty acid (FFA) release. Increased FFAs then contributes to insulin resistance by disrupting the signal transduction pathway of insulin mediated glucose disposal as well as cause impaired insulin secretion through pancreatic beta cell apoptosis. FFAs decrease insulin sensitivity through the induction of oxidative stress and the activation the serine kinases, protein kinase Cq (PKCq) and inhibitor kappa b kinase (IKKb), which are known mediators of inflammation [36]. In fact, both chronic over-nutrition (obesity) and T2DM may represent pro-inflammatory states as increased concentrations of tumour necrosis factor-alpha (TNF-α) in these conditions have been found to interfere with insulin action by suppressing insulin signal transduction [37, 38].

Compelling evidence from both the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) has shown that chronic hyperglycemia significantly increases the risks of developing complications such as nephropathy, neuropathy and retinopathy and tight glycaemic control is critical for the prevention of these complications [39]. One of the ways chronic hyperglycaemia contributes to the development of diabetic complications is through increased cellular oxidative stress. Diabetic neuropathy (DN) is one such example where the increased conversion of glucose to sorbitol *via* the sorbitol-aldose reductase pathway (polyol pathyway) by aldose reductase results in an accumulation of intracellular sorbitol [40]. It is also associated with decreased myoinositol due to a myo-inositol-related defect in nerve Na(+)-K(+)-ATPase, and decreased taurine levels (mechanism unclear) [41, 42]. The outcome of this metabolic alteration is a decreased NA+K+ ATPase activity, which in turns slows nerve conductivity [43]. Hence, in addition to hyperglycaemia and dyslipidaemia driven oxidative stress, the presence of polyol pathway activation and advanced glycated end products (AGEs), coupled to protein kinase C (PKC) activation account for the already complex network of interacting metabolic factors responsible for the endothelial dysfunction and reduced nerve perfusion and function [44].

Another way in which hyperglycaemia increases the risk of cellular oxidative damage is through a reduction in antioxidant defence [45], which has been observed during oral glucose challenge [46, 47]. Moreover, the conversion of glucose to sorbitol, and later fructose, results in the depletion of cellular nicotinamide adenine dinucleotide phosphate (NADPH) and oxidized nicotinamide adenine dinucleotide (NAD+) stores. This increases the vulnerability of the cell to the damaging actions of ROS. Furthermore, hyperglycaemia promotes the formation of ROS [48-50] by the autooxidation of glucose *via* the mitochondrial electron transport chain [51] and the formation of AGEs [52, 53].

In summary, hyperglycemia and increased FFA favours the generation of ROS and RNS, leading to increased oxidative stress. In the absence of an appropriate compensatory response from endogenous antioxidant defences, the system becomes overwhelmed (redox imbalance), leading to the activation of stress-sensitive signalling pathways, such as NF-kB, p38 mitogen-activated protein kinase (MAPK), Jun

kinases (JNK), stress-activated protein kinases (SAPK), PKC, AGE, receptor for advanced glycosylation end-products (RAGE) and sorbitol. Hence, oxidative stress, induced by high glucose load followed by activation of other pathways cause cellular damage, and are ultimately responsible for the long-term complications of diabetes [54].

TREATMENT OF INSULIN RESISTANCE

The current non-pharmacological avenues of increasing insulin sensitivity in T2DM are exercise and diet, with biguanides, sulphonylureas and thiazolidinediones as the mainstays of pharmacological treatment. Insulin is usually reserved for use in secondary failure of oral agents and in diabetic hyperglycaemic emergencies.

ALA has shown therapeutic potential in the area of insulin resistance [55]. A four-week placebo-controlled euglycaemic glucose-clamp study using oral ALA at 600 mg daily in patients with T2DM showed an improvement of insulin-stimulated glucose disposal of 27% compared to placebo [56]. This improvement in insulin sensitivity was also replicated in a more recent study using oral ALA at 600 mg twice a day [57]. Being a powerful antioxidant, ALA has shown some promise as a safe alternative in reducing insulin resistance through augmenting insulin stimulated glucose disposal, inhibiting inflammatory cytokines and decreasing ROS production [58-60].

Another important action of ALA is on the expression of AMP-activated protein kinase (AMPK) in the hypothalamus and peripheral tissues. AMPK functions as a fuel sensor in the cell and is activated when cellular energy is depleted reflected by an increase in AMP:ADP ratio [61]. AMPK activation in skeletal muscle improves insulin sensitivity by increasing glucose uptake and fatty acid oxidation. It does this by promoting glucose transport through the translocation of GLUT-4 to the plasma membrane in an insulin-independent manner [22]. Insulin sensitivity is also improved through the reduction in triglyceride accumulation in skeletal muscle [54]. This occurs as a result of AMPK phosphorylating, and thus inactivating acetyl-CoA carboxylase 2 (ACC-2 or β) leading to a decrease in malonyl-coenzyme A (malonyl-CoA). Decreased malonyl-CoA would thus cause an increase in long fatty chain acid oxidation [62, 63]. Interestingly, AMPK is also responsible for mediating the effects of the oral hypoglycaemic agents such as metformin and peroxisome proliferator-activated receptors (PPAR) gamma agonists [64]. Finally, ALA exerts potent anti-obesity effects by decreasing hypothalamic AMPK activity and reducing food intake thereby causing profound weight loss *in vivo* [65].

TREATMENT OF DIABETIC NEUROPATHY

One of the commonest complications developing in at least one-third of all patients is diabetic neuropathy (DN). Diabetic neuropathy is a dynamic and chronic degenerative disorder which commonly manifests as a distal symmetrical polyneuropathy. It has multiple interactive pathogenetic mechanisms including perfusion abnormalities and oxidative stresses [66], which explains the difficulty in designing efficacious and biologically-meaningful therapies [67]. The first step in the long-term treatment of DN is to aim for a stable and optimal glycaemic control. Common pharmacological treatment of DN includes the use of amitriptyline, anticonvulsants and opioids, which have been shown to alleviate the varied spectrum of symptoms like burning, paraesthesias and pain, but at the significant expense of adverse effects, and effective pain relief is reported to be achieved in less than half of patients with chronic neuropathic pain [68].

Several newer agents have been shown to be efficacious in randomized controlled trials, but with the exception of duloxetine and pregabalin, none has been specifically licensed for the management of painful DN [69, 70]. Even so, there was a higher drop rate in patients on duloxetine due to adverse events (13.9% *vs* 7.2%), suggesting that it should be used with similar caution like the other anti-depressants [71].

From the understanding so far of the conceptual framework of the multi-factorial pathogenesis and treatment of DN from animal studies and cell cultures, there is still no long term effective pathogenetic treatment for DN to date, although a few drugs are currently being studied in clinical trials. ALA, however, has shown much promise [72], and has already been used as treatment for DN in some European countries like Germany.

Given the lack of consensus concerning the appropriate first line treatment of neuropathic pain, due to a lack of head to head comparisons which limits any definitive conclusions in this area, clinicians must therefore make decisions regarding the care of individual patients using randomized trials with positive outcome for each agent [69, 72, 73].

One of the possible beneficial effects of ALA is on the improvement of microcirculation as it has been shown to increase perfusion reserve on demand as demonstrated by a decrease in the time to peak capillary blood cell velocity during post-occlusive hyperemia both orally (12.6 ± 3.1s *vs* 35.4 ± 10.9 s, $p<0.05$) and intravenously (11.74 ± 4.4s *vs* 21.9 ± 5.0 s, $p<0.05$) [74]. The authors suggested that this likely reflected an improvement of the pathophysiology of the nerves rather than an actual regeneration of nerve endings. Moreover, oral ALA 800mg/day for 4 months was also shown to have favourable effects on cardiac autoneuropathy in T2DM patients [75].

Several European studies have demonstrated the benefits of ALA in symptomatic polyneuropathy. In the (Alpha Lipoic Acid in Diabetic Neuropathy I) ALADIN-I study, intravenous ALA was shown to improve symptom scores [76] while the ALADIN-II study demonstrated meaningful dose-dependent improvements in neuropathic functions with oral ALA for a two-year duration, reflected as an improvement in sural sensory nerve conduction velocity (+3.8 ± 4.2 m/s *vs* -0.1 ± 4.8 m/s, $p<0.05$), sural sensory nerve action potential (+0.3 ± 1.4 V *vs* -0.7 ± 1.5 V, $p<0.05$) and in tibial motor nerve conduction velocity (+1.2 ± 3.8 m/s *vs* -1.5 ± 2.9 m/s, $p<0.05$) [77].

In the SYDNEY Trial, oral treatment with ALA 600mg thrice daily for three weeks or intravenous ALA 600mg infused five times per week were shown to improve symptoms on the Total Symptom Score (TSS), Hamburg Pain Adjective List (HPAL), Neuropathy Disability Score (NDS) and Neuropathic Impairment Score (NIS) as compared to placebo [78, 79].

Two multi-centre studies are now are underway to determine the role of ALA in the prevention and treatment of diabetic neuropathy. The Neurological Assessment of Thioctic Acid in Neuropathy I (NATHAN I) Study, is a pivotal long-term trial using oral ALA conducted in North America and Europe spanning four years and is aimed at slowing the progression of diabetic polyneuropathy, while NATHAN II addresses the use of an intravenous agent for symptomatic relief of painful neuropathy [80].

ADVERSE EFFECTS

In terms of side effect profile, the SYDNEY-2 trial demonstrated a dose-dependent increase in nausea, vomiting, and vertigo with increasing doses of ALA from 600mg up to a maximum of 1800mg. Hence, an oral dose of 600mg once daily was recommended by the investigators in order to provide the optimal risk-benefit ratio [81].

The risk of hypoglycaemia with the use of ALA has been attributed to an autoimmune process called Insulin Autoimmune Syndrome (IAS), in addition to potentiating the effects of other hypoglycaemic agents like insulin therapy [82, 83]. IAS (also known as Hirata's disease) was first described in 1970 and is a relatively rare cause of hypoglycaemia [84]. It is characterized by the production of auto-antibodies to insulin in individuals who have not previously been exposed to insulin. Another risk factor for the development of this complication is the use of sulfydryl drugs like methimazole, mercaptopropionyl glycine and glutathione. It is therefore believed that IAS is a form of drug-induced autoimmunity as a result of drug-drug interaction because ALA, being a disulphide derivative, has the ability to also produce a sulfydryl group when reduced *in vivo* [85]. Finally, the risk is also higher in East Asians and certain North American natives, among whom the prevalence of HLA alleles that confer predisposition to this syndrome is relatively high [86].

CONCLUSION

New headways are currently being forged in the understanding of the pathogenesis of T2DM and its complications. Specific targeted therapy by ALA has been shown to be both an attractive and relevant adjuvant pharmacotherapy for DN [87]. Given the growing evidence of increased oxidative and inflammatory load implicated in T2DM, treatment paradigms may have to shift to target these stressors with the use of compounds like ALA. Adequately powered randomized placebo controlled trials are urgently needed to establish its role in the treatment of hyperglycemia and DN in T2DM. For example, given that ALA is rapidly metabolized and excreted with peak plasma concentrations lasting less than an hour, the clinical and long term value of ALA in improving glycaemic control as reflected by the glycated haemoglobin (HbA1c) levels need to be established [27].

Although a change in lifestyle is the best preventive and therapeutic approach, ALA may prove to be an important part of the therapeutic armamentarium in combating the worldwide epidemic of diabetes, along with other established arms of treatment. In conclusion, the use of ALA represents a potential and attractive pharmacological target in the treatment of T2DM by modulating the signal transduction pathways in insulin resistance and antagonizing the oxidative and inflammatory stresses, which are major players in the pathogenesis of this disorder.

ABBREVIATIONS

ACC-2 or β	=	Acetyl-CoA Carboxylase 2
AGEs	=	Advanced Glycated End products
ALADIN-I	=	Alpha Lipoic Acid in Diabetic Neuropathy I
ALADIN-II	=	Alpha Lipoic Acid in Diabetic Neuropathy II
ALA	=	Alpha Lipoic Acid
AMPK	=	AMP-activated Protein Kinase
CCl4	=	Carbon Tetrachloride
DCCT	=	Diabetes Control and Complications Trial
DHLA	=	Dihydrolipoic Acid
DN	=	Diabetic Neuropathy
ESRF	=	End-Stage Renal Failure
FFA	=	Free Fatty Acid
GLUT	=	Glucose Transporter
HPAL	=	Hamburg Pain Adjective List
IAS	=	Insulin Autoimmune Syndrome
IKKb	=	Inhibitor *of nuclear factor* Kappa b Kinase
IR	=	Insulin Receptors
JNK	=	Jun Kinases
MAPK	=	Mitogen-Activated Protein Kinase
Malonyl-CoA	=	Malonyl-Coenzyme A
NAD+	=	Nicotinamide Adenine Dinucleotide
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate
NATHAN I	=	Neurological Assessment of Thioctic Acid in Neuropathy I
NATHAN II	=	Neurological Assessment of Thioctic Acid in Neuropathy II
NDS	=	Neuropathy Disability Score
NF-kB	=	Nuclear Factor-Kappa B
NIS	=	Neuropathic Impairment Score
PKC	=	Protein Kinase C
PKCq	=	Protein Kinase Cq
PPAR	=	Peroxisome Proliferator-Activated Receptor
R-LA	=	R-enantiomer *of* Lipoic Acid
RAGE	=	Receptor for Advanced Glycosylation End-product
ROS	=	Reactive Oxygen Species

RNS	=	Reactive Nitrogen Species
S-LA	=	S-enantiomer *of* Lipoic Acid
SAPK	=	Stress-Activated Protein Kinase
TNF-α	=	Tumour Necrosis Factor-Alpha
TSS	=	Total Symptom Score
T2DM	=	Type 2 Diabetes Mellitus
UKPDS	=	United Kingdom Prospective Diabetes Study

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